A 56-year-old woman with sarcoidosis and acute renal failure

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CASE PRESENTATION

A 56-year-old Hispanic woman with a history of sarcoidosis came to the Emergency Department complaining of bilateral leg pain. One year before admission, she had presented to another hospital with shoulder pain and weight loss. At that time, she was found to have hypercalcemia and acute renal failure. Computed tomography of the chest revealed mediastinal and hilar lymphadenopathy, and a transbronchial needle biopsy was consistent with sarcoidosis. She was treated with intravenous fluids, a bisphosphonate, and steroids, which were tapered off over 2 months. Her creatinine level decreased from 4.5 to 1.3 mg per 100 ml. One month before admission, she had been checked by a primary care doctor for a routine visit, and lab tests included a creatinine level of 5.1 mg per 100 ml. Past medical history was also notable for hypertension and a hysterectomy. Her medications included amlodipine and intermittent naproxen (she reported only having taken four pills recently of naproxen).

Physical examination revealed a well-appearing woman. The blood pressure was 132/82 and there was mild diffuse tenderness on palpation of her legs bilaterally. There was no rash. Her lungs were clear. The heart was regular in rate and rhythm with no murmurs, rubs, or gallops. No lymphadenopathy or hepatosplenomegaly was appreciated. There was no lower extremity edema. Laboratory values and radiology results are shown in Table 1. She was initially treated with intravenous fluids and furosemide. Her calcium level was normalized, but her creatinine level continued to rise. A renal biopsy was performed.

RENAL BIOPSY FINDINGS

Of the 10 glomeruli sampled, 3 were globally sclerotic. Four glomeruli located in zones of interstitial fibrosis displayed global mild retraction of the tuft with wrinkling of glomerular basement membranes and Bowman's capsular sclerosis. The remaining glomeruli were unremarkable. The cortical interstitium was diffusely expanded by moderate-to-severe fibrosis, edema, and inflammation. The interstitial leukocytes consisted of lymphocytes, monocytes, and numerous multinucleated giant cells forming multifocal granulomas (Figure 1). The granulomas ranged from small to large and from discrete to confluent, without evidence of central necrosis or caseation (Figure 2). Most giant cells were of the Langhans type, some containing birefringent asteroid bodies and calcified basophilic Schaumann bodies (Figure 3). There was focal tubulitis with tubular degenerative and regenerative changes. Tubular atrophy affected 60% of the cortex. There was moderate arteriosclerosis and arteriolosclerosis.

Special stains (acid fast bacilli and Gomori methenamine silver) were negative for acid fast bacilli and fungal organisms. Routine immunofluorescence was negative for immunoglobulins and complement in all compartments, with the exception of granular staining for C3 involving some tubular basement membranes. By electron microscopy, the glomeruli were unremarkable. The interstitium displayed granulomatous inflammation including giant cells that contained electron-dense concretions consistent with Schaumann bodies. There was focal lymphocytic tubulitis and acute tubular injury. No tubulo-interstitial electron-dense deposits were identified.

PATHOLOGIC DIAGNOSIS

Granulomatous interstitial nephritis (GIN), severe, active, and chronic, was consistent with renal sarcoidosis. Arteriosclerosis was moderate.

CLINICAL FOLLOW-UP

The patient was started on prednisone 100 mg day^{-1}, amlodipine 2.5 mg day^{-1}, and subcutaneous epoetin alpha 14 000 U three times weekly. At 2 weeks, the prednisone was tapered to 100 mg every other day, and mycophenolate mofetil (MMF) 500 mg twice daily was added. Figure 4 shows the time course of the patient's serum creatinine and serum

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Table 1 | Diagnostic tests on admission

	Value (reference range)
Serum/blood	
Urea nitrogen	44 mg per 100 ml (7–20 mg per 100 ml)
Creatinine	8.9 mg per 100 ml (0.5–0.9 mg per 100 ml)
Calcium	14.1 mg per 100 ml (8.4–9.8 mg per 100 ml)
Phosphorus	6.7 mg per 100 ml (2.5–4.3 mg per 100 ml)
White blood cells	$9.4 \times 10^9\,l^{-1}$ ($3.54–9.06 \times 10^9\,l^{-1}$)
Hemoglobin	9.9 g per 100 ml (12.0–15.8 g per 100 ml)
Hematocrit	28.3% (35.4–44.4%)
Platelets	$455 \times 10^9\,l^{-1}$ ($165–415 \times 10^9\,l^{-1}$)
Total protein	8.0 g per 100 ml (6.7–8.6 g per 100 ml)
Albumin	3.6 g per 100 ml (4.0–5.0 g per 100 ml)
Urine	
Urinalysis	Negative for blood and protein
Microscopy	3 WBC hpf^{-1}, 0–3 RBC hpf^{-1}, 1+ triple phosphate crystals (0–3 WBC hpf^{-1}, 0–3 RBC hpf^{-1})
24-h protein	1071 mg (50–150 mg)
Urine protein electrophoresis	Negative
Serologic tests	
Angiotensin-converting enzyme	231 U l^{-1} (0–90 U l^{-1})
Serum protein electrophoresis	Negative
Hepatitis B surface antigen	Negative
Hepatitis C antibody	Negative
Radiology	
Chest radiograph	Fine reticular pattern at the bilateral lung bases, left greater than right
Renal ultrasound	Normal echogenicity; right kidney 9.0 cm; left kidney 9.2 cm, with small nonobstructing calculus

hpf, high-powered field.

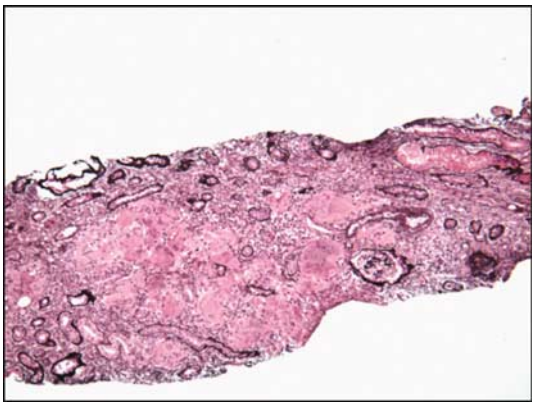

Figure 1 | A low power view shows the widespread effacement of tubulo-interstitial architecture by confluent granulomatous inflammation and interstitial fibrosis, causing broad separation and focal loss of tubular basement membranes (Jones methenamine silver, original magnification $\times$ 100).

calcium over the first 15 days following presentation. At 1 month, her creatinine level had decreased to 2.2 mg per 100 ml. Amlodipine was changed to ramipril, and epoetin-α

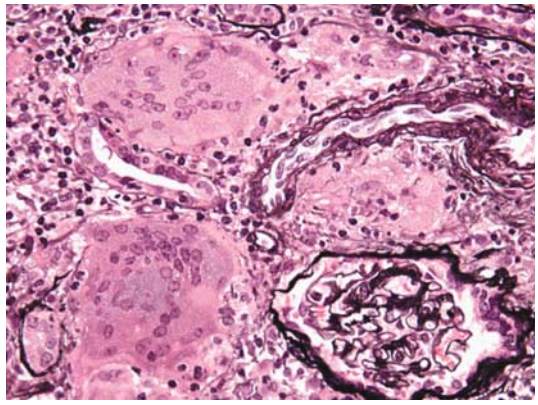

Figure 2 | This field shows several small discrete granulomas containing multinucleated giant cells surrounded by lymphocytic infiltrates, without evidence of caseation or central necrosis. The adjacent glomerulus displays thickening of its Bowman's capsule, but it is otherwise unremarkable (Jones methenamine silver, original magnification $\times$ 400).

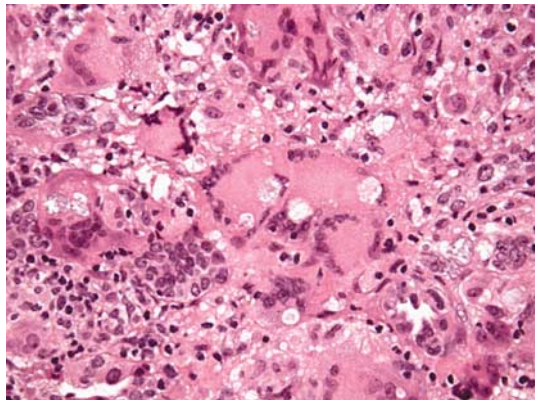

Figure 3 | Many of the interstitial giant cells contain intracytoplasmic inclusions, some of which are basophilic, consistent with Schaumann bodies. Under polarized light (not illustrated), some of the stellate inclusions were birefringent, consistent with asteroid bodies (hematoxylin and eosin, original magnification $\times$ 400).

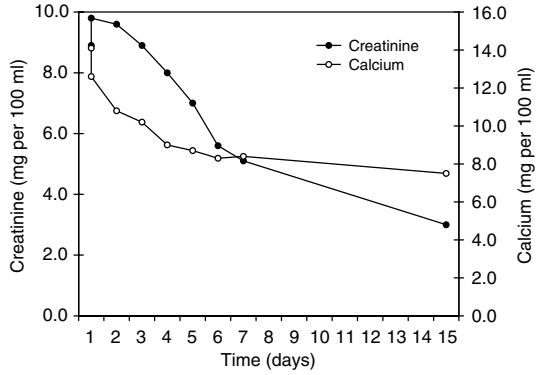

Figure 4 | The patient's serum creatinine (closed circles, solid line) and serum calcium (open circles, dashed line) are plotted against time for the first 15 days following presentation. Renal biopsy was performed on day 2.

Table 2 | Renal manifestations of sarcoidosis

Calcium dysregulation
Hypercalciuria
Hypercalcemia
Renal tubular acidosis
Nephrolithiasis
Obstructive uropathy
Retroperitoneal lymphadenopathy
Retroperitoneal fibrosis
Tubulointerstitial disease
Nephrocalcinosis
Granulomatous interstitial nephritis
Non-granulomatous interstitial nephritis
Glomerular disease (rare, association unclear)
Minimal change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
IgA nephropathy
Membranoproliferative glomerulonephritis
Proliferative and crescentic glomerulonephritis
ANCA-positive crescentic glomerulonephritis

was discontinued. At 2 months, the prednisone was decreased to 80 mg every other day, and then slowly tapered to off over the next 3 months. MMF was changed to mycophenolate sodium because the patient complained of abdominal pain and diarrhea. The mycophenolate sodium was titrated up to 720 mg twice daily, and she remained asymptomatic on this dose. At her most recent follow-up, 18 months after the biopsy, the creatinine level was 1.8 mg per 100 ml.

DISCUSSION

Sarcoidosis is a multisystem disorder of unknown etiology, characterized by granuloma formation. Most commonly, it affects the lungs, skin, and eyes, but it can impact all organs, including the kidney. Although clinically apparent renal involvement is considered rare, one series found renal abnormalities of various types in 48% of patients with chronic sarcoidosis (but none with acute sarcoidosis).[1] A summary of the renal manifestations of sarcoidosis is presented in Table 2.

The most common renal manifestation is related to abnormal calcium metabolism. In patients with sarcoidosis, the incidence of hypercalcemia is 10–20% and that of hypercalciuria is 40–50%.[2] The cause of hypercalcemia is 1-hydroxylation of 25(OH) vitamin D to form $1,25(OH)_2$ vitamin D in the macrophages of sarcoid granulomas.[3] This leads to increased intestinal absorption of calcium, increased bone resorption, and calciuria (with or without hypercalcemia). Hypercalciuria can lead to acute renal failure by causing concentrating defects, nephrocalcinosis, or nephrolithiasis; renal function may be further impaired by hypercalcemia-induced vasoconstriction, decreasing glomerular filtration rate, and causing tubular ischemia. Irreversible renal damage from nephrocalcinosis is rare, occurring in less than 2% of patients.[2] In addition to the tubular effects of calcium metabolism, renal tubular acidosis and inappropriate glucosuria can be present.[4]

Nephrolithiasis occurs in up to 15% of patients with sarcoidosis, and in approximately 4% of patients, it may be the presenting feature of the disease.[5,6] Obstructive uropathy may result from nephrolithiasis, but in patients with sarcoidosis, obstruction may also be due to retroperitoneal fibrosis or lymphadenopathy leading to ureteral obstruction.[7]

Primary glomerular disease in patients with sarcoidosis is rare. However, there are case reports associating sarcoidosis with minimal-change disease, focal segmental glomerulosclerosis, membranous nephropathy, IgA nephropathy, membranoproliferative glomerulonephritis, proliferative and crescentic glomerulonephritis, and Anti-neutrophil cytoplasmic antibodies (ANCA)-positive crescentic glomerulonephritis.[8] The mechanism for glomerular involvement of sarcoidosis is unclear, and a causal relationship has not been proven.

A more common manifestation of sarcoidosis in the kidney is granulomatous infiltration of the renal parenchyma. Although autopsy studies reveal granulomas in the kidneys of 20% of patients with sarcoidosis,[9] clinically significant disease related to granuloma formation is less common and difficult to prove due to the frequent coexistence of nephrocalcinosis. In a series of 46 patients with sarcoidosis, 15 had renal abnormalities. Of the 10 biopsied, 6 had nephrocalcinosis, 2 had GIN, 1 had non-GIN, and 1 had GIN and IgA-nephropathy.[1] Table 3 summarizes some of the larger adult case series of GIN from sarcoidosis.

The pathologic findings of GIN consist of interstitial collections of epitheliod histiocytes, giant cells, and lymphocytes forming granulomas. In sarcoidosis, the granulomas are small, well defined, and noncaseating. The presence of Schaumann bodies (laminated intracytoplasmic concretions) within the granulomas is pathognomonic for sarcoidosis. Immunofluorescence or electron microscopic studies are unrevealing.[18]

The differential diagnosis for GIN is broad. The most common etiology is allergic (drug-induced) (25–45%), followed by sarcoidosis (9–29%). Other causes include Wegeners granulomatosis (8–16%), infections (9–25%), foreign-body giant cell reaction, and tubulointerstitial nephritis and uveitis syndrome. Drugs that are particularly related to GIN include β-lactam antibiotics and anticonvulsants. Tuberculosis is the most common infection related to GIN, although fungal pyelonephritis, for instance related to histoplasmosis, has been reported, particularly in immunocompromised patients.[19,20] There have also been associations reported between sarcoidosis and tubulointerstitial nephritis and uveitis syndrome, a condition usually affecting young women, manifested by renal and bone marrow granulomas and uveitis.[21]

Rarely, renal sarcoidosis may lead to end-stage renal disease, most commonly with severe nephrocalcinosis. A review of five patients with renal sarcoidosis leading

Table 3 | Comparison of case series of sarcoidosis-related granulomatous interstitial nephritis

Author	Average age (range)	Number of patients (M/F)	Range of proteinuria (g day^{-1})	Percent with hematuria	Average initial creatinine, mg per 100 ml (range)	Average initial calcium level, mg per 100 ml (range)	Range of initial dose of prednisone	Average length of steroid treatment, years (range)	Average creatinine after steroids, mg per 100 ml (range)	Percent relapse	Latest creatinine, mg per 100 ml (range)
Simonsen[10]	59 (45–68)	5 (2/3)	NA	NA	7.4 (2.0–15.8)[a]	NA	NA	NA	2.9 (2.3–3.9)[b]	25%	NA
Hannedouche[11]	63 (41–82)	6 (3/3)	0.4–1.0	33%	6.1 (3.1–9.7)	10.0 (8.6–10.8)	30 mg day^{-1} to 1 mg kg^{-1} day^{-1}	2.9 (1–7)	2.1 (1.8–3.3)	67%	3.2 (1.8–4.4)
Duvic[12]	40 (22–74)	6	0–0.7	17%	2.7 (1.6–5.5)	10.4 (9.6–12.2)	0.7–1 mg kg^{-1} day^{-1}	NA (1–6)	NA (4/6 steroid sensitive)	NA	NA
O'Riordan[13]	NA	5 (3/2)	Present but not quantified	NA	10.4 (2–20)[c] CrCl (ml min^{-1})	NA	0.5–1 mg kg^{-1} day^{-1}	NA	NA	20%	25 (18–40)[c] CrCl (ml min^{-1})
Brause[14]	60 (48–74)	5 (3/2)	0–0.5	NA	3.8 (1.9–6.4)	10.4 (9.6–12.9)	1 mg kg^{-1} day^{-1}	2.7 (0.5–5)	2.0 (1.1–2.8)	0%	NA
Robson[15]	64 (35–72)	7 (5/2)	0–0.8	NA	15.7 (6–29)[c] CrCl (ml min^{-1})	NA	20–500 mg	NA	30.3 (14–56)[c] CrCl (ml min^{-1})	29% relapse, 29% steroid resistant	31.2 (21–53)[c] CrCl (ml min^{-1})+ 2 patients on dialysis
Carmichael[16]	59 (41–71)	6 (3/3)	0–3.6	83%	4.4 (2.1–7.7)	11.6 (9.0–14.2)	30–60 mg day^{-1}	NA	1.7 (0.9–2.9)	50%	1.5 (0.9–2.4)
Javaud[17]	52 (29–76)	20 (12/8)	0.08–1.9	0%	30 (5.9–70)[c] CrCl (ml min^{-1})	NA, but 20% were hypercalcemic ($>$2.6 mmol l^{-1})	1 mg kg^{-1} day^{-1}	2.2 (0.25–5)	NA	NA	48 (10–97)[c] CrCl (ml min^{-1})+1 patient on dialysis

CrCl, creatinine clearance; M/F, male/female; NA, data not available.
[a]Data available for four of five patients.
[b]Data available for three of five patients.
[c]Data reported as creatinine clearance instead of creatinine.

to end-stage renal disease and kidney transplantation found that two of the patients developed recurrent disease in the graft, in both cases successfully managed with corticosteroids.[22]

The standard treatment for sarcoidosis has been corticosteroids, usually started at the equivalent of prednisone 1 mg kg^{-1} day^{-1}. As shown in Table 3, there is usually an impressive response, but relapses are frequent, particularly when steroids are tapered. These relapses usually respond to reinitiation of steroids, but most patients are left with chronic renal dysfunction from interstitial fibrosis. In a recent series of 17 patients with sarcoid granulomatous nephritis, all were treated initially with prednisolone 0.5 mg kg^{-1} day^{-1} and then tapered to maintenance doses of 5–7.5 mg day^{-1}. Three of 17 (18%) relapsed upon ceasing therapy and responded to reinitiation of corticosteroids, 1 (6%) ceased therapy and was lost to follow-up and represented an end-stage renal failure, and 2 (12%) had multiple relapses and were successfully managed with the addition of mycophenolate mofetil and azathioprine, respectively.[23]

Patients who are steroid-intolerant or steroid-resistant have been treated with cyclophosphamide, infliximab, azathioprine, and MMF with varying degrees of success.[16,23–26] In a case series of six patients, the addition of azathioprine to a steroid regimen enabled the taper of prednisone to 5–7.5 mg day^{-1} in four of five patients.[16]

Mycophenolate mofetil has been used to treat nonrenal sarcoidosis. One patient with uveitis from sarcoidosis improved when MMF was added to his preexisting regimen of steroids and cyclosporine.[27] Five patients with mucocutaneous sarcoidosis (although without renal manifestations) who either were steroid-intolerant or had steroid-resistant disease were successfully treated with MMF.[28] There is a report of a patient with ANCA-negative crescentic glomerulonephritis associated with duodenal and pancreatic sarcoidosis with recurrent duodenitis and pancreatitis with each attempt at steroid taper. MMF was started and enabled a prednisone taper to 4 mg day^{-1}. The patient remained in remission at 15 months, at which time MMF was discontinued.[29] MMF has been added to steroid regimens in two case series of renal sarcoidosis (four patients in total) to enable steroid tapering to low doses.[16,30] There has been only one case report of renal-limited sarcoidosis being successfully treated with MMF monotherapy. This patient, a 15-year-old boy, presented with a creatinine level of 7.2 mg per 100 ml. He was treated with pulsed solumedrol for 3 days, followed by prednisone 40 mg twice daily for 2 months, then 60 mg daily for 1 month, at which time his creatinine level had decreased to 1.4 mg per 100 ml. At this point, MMF was added as a steroid-sparing agent, and titrated up to 1000 mg twice daily. Steroids were tapered to off over the following 4 months, and his creatinine level remained at 1.1 mg per 100 ml. At 1 year, the MMF was decreased to 500 mg twice daily and benazepril was added. His creatinine level was 1.1 mg per 100 ml at 21 months after disease onset.[25]

CONCLUSION

In summary, renal failure from sarcoid-related GIN is uncommon. When it occurs, it is almost always sensitive to steroids, but tends to relapse when steroids are tapered. There are few data on steroid-sparing regimens in patients with relapsing sarcoidosis, and MMF and azathioprine may be considered in this situation.

REFERENCES

1. Bergner R, Hoffmann M, Waldherr R *et al.* Frequency of kidney disease in chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2003; **20**: 126–132.
2. Studdy PR, Bird R, Neville E *et al.* Biochemical findings in sarcoidosis. *J Clin Pathol* 1980; **33**: 528–533.
3. Fuss M, Pepersack T, Gillet C *et al.* Calcium and vitamin D metabolism in granulomatous diseases. *Clin Rheumatol* 1992; **11**: 28–36.
4. Muther RS, McCarron DA, Bennett WM. Granulomatous sarcoid nephritis: a cause of multiple renal tubular abnormalities. *Clin Nephrol* 1980; **14**: 190–197.
5. Lancina Martin JA, Garcia Freire C, Busto Castanon L *et al.* [Sarcoidosis and urolithiasis]. *Arch Esp Urol* 1995; **48**: 234–239.
6. Rizzato G, Colombo P. Nephrolithiasis as a presenting feature of chronic sarcoidosis: a prospective study. *Sarcoidosis Vasc Diffuse Lung Dis* 1996; **13**: 167–172.
7. Gobel U, Kettritz R, Schneider W *et al.* The protean face of renal sarcoidosis. *J Am Soc Nephrol* 2001; **12**: 616–623.
8. Appel GB, Radhakrishnan J, D'Agati V. Secondary glomerular diseases. In: Brenner BM, Rector FC (eds). *Brenner & Rector's The Kidney*, 7th edn. Saunders: Philadelphia, PA, 2004, pp 1382–1482.
9. Sheffield EA. Pathology of sarcoidosis. *Clin Chest Med* 1997; **18**: 741–754.
10. Simonsen O, Thysell H. Sarcoidosis with normocalcemic granulomatous nephritis. Five case reports and a review of 24 cases in the literature. *Nephron* 1985; **40**: 411–417.
11. Hannedouche T, Grateau G, Noel LH *et al.* Renal granulomatous sarcoidosis: report of six cases. *Nephrol Dial Transplant* 1990; **5**: 18–24.
12. Duvic C, Herody M, Rossignol P *et al.* Les manifestations renales de la sarcoidose. A propos de neuf observations. *Rev Med Interne* 1999; **20**: 226–233.
13. O'Riordan E, Willert RP, Reeve R *et al.* Isolated sarcoid granulomatous interstitial nephritis: review of five cases at one center. *Clin Nephrol* 2001; **55**: 297–302.
14. Brause M, Magnusson K, Degenhardt S *et al.* Renal involvement in sarcoidosis—a report of 6 cases. *Clin Nephrol* 2002; **57**: 142–148.
15. Robson MG, Banerjee D, Hopster D *et al.* Seven cases of granulomatous interstitial nephritis in the absence of extrarenal sarcoid. *Nephrol Dial Transplant* 2003; **18**: 280–284.
16. Carmichael P, O'Donnell JP. The protean face of renal sarcoid. *J Nephrol* 2003; **16**: 721–727.
17. Javaud N, Belenfant X, Stirnemann J *et al.* Renal granulomatoses: a retrospective study of 40 cases and review of the literature. *Medicine (Baltimore)* 2007; **86**: 170–180.
18. D'Agati VD, Jennette JC, Silva FG. Noninfectious tubulointerstitial nephropathies. *Non-Neoplastic Kidney Diseases. Fascicle 4 of the Atlas of Nontumor Pathology*. American Registry of Pathology: Washington, DC, 2005, pp 590–591.
19. Bijol V, Mendez GP, Nose V *et al.* Granulomatous interstitial nephritis: a clinicopathologic study of 46 cases from a single institution. *Int J Surg Pathol* 2006; **14**: 57–63.
20. Nasr SH, Koscica J, Markowitz GS *et al.* Granulomatous interstitial nephritis. *Am J Kidney Dis* 2003; **41**: 714–719.
21. Sessa A, Meroni M, Battini G *et al.* Acute renal failure due to idiopathic tubulo-intestinal nephritis and uveitis: 'TINU syndrome'. Case report and review of the literature. *J Nephrol* 2000; **13**: 377–380.
22. Padilla ML, Schilero GJ, Teirstein AS. Sarcoidosis and transplantation. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; **14**: 16–22.
23. Rajakariar R, Sharples EJ, Raftery MJ *et al.* Sarcoid tubulo-interstitial nephritis: long-term outcome and response to corticosteroid therapy. *Kidney Int* 2006; **70**: 165–169.
24. Dimitriades C, Shetty AK, Vehaskari M *et al.* Membranous nephropathy associated with childhood sarcoidosis. *Pediatric Nephrol* 1999; **13**: 444–447.
25. Moudgil A, Przygodzki RM, Kher KK. Successful steroid-sparing treatment of renal limited sarcoidosis with mycophenolate mofetil. *Pediatric Nephrol* 2006; **21**: 281–285.
26. Ahmed MM, Mubashir E, Dossabhoy NR. Isolated renal sarcoidosis: a rare presentation of a rare disease treated with infliximab. *Clin Rheumatol* 2007; **8**: 1346–1349.
27. Kilmartin DJ, Forrester JV, Dick AD. Rescue therapy with mycophenolate mofetil in refractory uveitis. *Lancet* 1998; **352**: 35–36.
28. Kouba DJ, Mimouni D, Rencic A *et al.* Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis.[see comment]. *Br J Dermatol* 2003; **148**: 147–148.
29. O'Connor AS, Navab F, Germain MJ *et al.* Pancreatitis and duodenitis from sarcoidosis: successful therapy with mycophenolate mofetil. *Dig Dis Sci* 2003; **48**: 2191–2195.
30. Richmond JM, Chambers B, D'Apice AJ *et al.* Renal disease and sarcoidosis. *Med J Aust* 1981; **2**: 36–37.